PEDIATRIC CARDIOLOGY

Acute Hemodynamic Effects of Increasing Hemoglobin Concentration in Children With a Right to Left Ventricular Shunt and Relative Anemia

ROBERT H. BEEKMAN, MD, FACC, DWIGHT T. TUURI, MD, FACC

Dayton, Ohio

The short-term effects of increasing hemoglobin concentration were evaluated at cardiac catheterization in seven children (aged 0.3 to 7.5 years) with a right to left ventricular shunt and relative anemia. Diagnoses were tetralogy of Fallot in six and L-transposition of the great vessels with ventricular septal defect and pulmonary stenosis in one. Before and 20 minutes after isovolumic partial exchange transfusion with 20 ml/kg packed red cells, the following variables were measured: hemoglobin, partial pressure of oxygen (Po_2), oxygen consumption, oxygen saturation and pressure in the aorta, superior vena cava and right and left atria. After partial exchange transfusion, hemoglobin increased from 13.7 ± 0.5 to 16.4 ± 0.4 g/100 ml ($p < 0.001$, mean ± SEM). Aortic Po_2 increased from 55.0 ± 3.5 to 62.0 ± 4.1 mm Hg ($p < 0.01$) and aortic oxygen saturation increased from 84.3 ± 2.3 to 90.9 ± 1.3% ($p < 0.002$). Effective pulmonary blood flow increased by 17% from 2.72 ± 0.10 to 3.17 ± 0.10 liters/min per m^2 ($p < 0.01$), and right to left shunt decreased by 59% from 1.44 ± 0.29 to 0.59 ± 0.10 liters/min per m^2 ($p < 0.01$). Systemic oxygen transport increased from 658 ± 48 to 738 ± 46 ml/min per m^2 ($p < 0.002$). After partial exchange transfusion, systemic vascular resistance increased from 15.9 ± 1.1 to 20.0 ± 1.4 units ($p < 0.01$). A significant relation was found between the percent increase in systemic resistance and both the percent decrease in right to left shunt ($y = 20.44x^{0.32}$, $r = 0.90$, $p < 0.01$) and the percent increase in Po_2 ($y = 0.36x + 2.88$, $r = 0.83$, $p < 0.02$).

Thus, an increased hemoglobin concentration in seven children with right to left ventricular shunt and relative anemia decreased the right to left shunt and increased effective pulmonary blood flow, aortic oxygen saturation, Po_2 and oxygen transport. These short-term effects appear to be related to the increase in systemic resistance after partial exchange transfusion. Correction of relative anemia in children with a right to left ventricular shunt may have significant hemodynamic benefits.

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The development of polycythemia is a normal compensatory response to chronic arterial hypoxemia which serves to increase blood oxygen carrying capacity and improve tissue oxygen delivery (1,2). A number of children with cyanotic congenital heart disease, however, may develop a state of relative anemia wherein the hemoglobin concentration is suboptimal for the degree of hypoxemia that is present. Subjective clinical improvement has been described (3–5) in such children after blood transfusion or iron therapy. Nevertheless, the physiologic consequences of relative anemia in children with cyanotic heart disease have not been studied. The purpose of this investigation was to evaluate the short-term hemodynamic effects of increasing the hemoglobin concentration in children with hypoxemia due to a right to left ventricular shunt and an initial hemoglobin value of less than 15 g/100 ml.

Methods

Patients. Seven children undergoing diagnostic cardiac catheterization for cyanotic congential heart disease served as the subjects of this investigation. As criteria for entry into the study, each child had systemic arterial hypoxemia due to a right to left ventricular shunt (ventricular septal defect and pulmonary stenosis) and a central venous hemoglobin concentration of less than 15 g/100 ml. The latter value was chosen because it approximates the upper limit of normal hemoglobin concentration (mean + 2 standard deviations) during the first 10 years of life and, as such,

From the Division of Cardiology, Department of Pediatrics, Wright State University School of Medicine, The Children's Medical Center, Dayton, Ohio. This study was supported in part by the Miami Valley Chapter of the American Heart Association, Dayton, Ohio. Manuscript received June 5, 1984; revised manuscript received September 4, 1984, accepted September 20, 1984.

Current address and address for reprints: Robert H. Beekman, MD, Division of Pediatric Cardiology, Box 66, C. S. Mott Children's Hospital, Ann Arbor, Michigan 48109.

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Table 1. Pertinent Clinical and Hemodynamic Data in Seven Children With a Right to Left Ventricular Shunt Before and After Isovolumic Partial Exchange Transfusion

			Hemoglobin (g/100 ml)		Flows (liters/min per m²): Systemic		Flows: Effective Pulmonary		Flows: Right to Left		Systemic Resistance (units)		Aortic Po_2 (mm Hg)		Aortic O_2 Saturation (%)		Systemic O_2 Transport (ml/min per m²)	
Case	Age (yr)	Diagnosis	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	0.3	ToF	14.8	16.6	5.50	4.43	2.50	3.38	3.00	1.05	11.5	16.3	39	46	72	85	803.3	856.2
2	0.5	ToF	12.2	16.7	3.48	3.79	2.40	3.03	1.08	0.76	18.7	19.5	47	51	81	88	472.6	559.2
3	0.9	ToF	14.1	16.0	3.51	3.70	2.76	3.33	0.75	0.37	15.7	17.6	63	69	87	91	592.2	740.3
4	1.8	ToF	13.3	16.0	4.55	4.02	3.22	3.57	1.33	0.45	12.3	16.2	55	63	88	93	731.8	821.1
5	4.1	ToF	14.8	17.7	4.38	3.56	2.69	3.00	1.69	0.56	16.2	24.7	61	77	87	94	775.0	813.8
6	5.4	ToF	11.9	14.6	3.64	3.07	2.77	2.80	0.87	0.27	19.5	24.1	65	69	90	94	537.3	579.4
7	7.5	L-TGA, VSD, PS	14.6	17.0	4.08	3.75	2.72	3.07	1.36	0.68	17.2	21.9	55	59	85	91	695.3	795.6
Mean			13.7	16.4	4.16	3.76	2.72	3.17	1.44	0.59	15.9	20.0	55.0	62.0	84.3	90.9	658.2	737.9
± SEM			0.5	0.4	0.27	0.16	0.10	0.10	0.29	0.10	1.1	1.4	3.5	4.1	2.3	1.3	47.5	45.5
p Value			< 0.001		0.08		< 0.01		< 0.01		< 0.01		< 0.01		< 0.002		< 0.002	

L-TGA = L-transposition of the great vessels; Post = after partial exchange transfusion; Pre = before partial exchange transfusion; PS = pulmonary stenosis; SEM = standard error of the mean; ToF = tetralogy of Fallot; VSD = ventricular septal defect.

excludes the presence of significant polycythemia in these children (6,7).

Pertinent clinical and hemodynamic data are presented in Table 1. There were four male and three female children ranging in age from 0.3 to 7.5 years; six had tetralogy of Fallot and one had L-transposition of the great vessels with ventricular septal defect and pulmonary stenosis. One patient (Case 6) had undergone a palliative surgical right ventricular outflow patch without closure of the ventricular septal defect, but had persistent severe pulmonary stenosis. No patient had pulmonary atresia, patent ductus arteriosus or significant aortopulmonary collateral vessels or other evidence of left to right shunt. Patient 7 had congenital complete heart block. Red blood cell indexes suggested iron deficiency in one child (Case 2, mean corpuscular volume 69 cu μ) and were normal in the remaining six. Detailed hematologic evaluation was not performed.

Measurements. Informed consent for cardiac catheterization and blood transfusion study was obtained for all patients. A complete right and left heart catheterization was performed in each patient. In six (Cases 1 to 5 and 7), however, the pulmonary arteries were not entered because of concern that additional right ventricular outflow obstruction might promote increased right to left shunting. Mixed venous oxygen saturation was determined from superior vena cava blood samples. Pulmonary venous oxygen saturation was measured through a patent foramen ovale in four patients, was estimated from systemic ventricular samples in two patients whose oxygen saturation in the apex of this chamber exceeded 95% and was assumed to be 95% in one patient. Blood oxygen content was determined as the sum of hemoglobin-bound and dissolved oxygen. Hemoglobin oxygen saturation was measured (AO Unistat oximeter), and dissolved oxygen (partial pressure of oxygen [Po_2] × 0.003) and oxygen-carrying capacity (hemoglobin × 1.36) were calculated. Oxygen consumption was measured in five patients using a continuous flow-through system (8) and in two by Douglas bag collection. Effective pulmonary and systemic blood flow, right to left shunt and systemic resistance were calculated in accordance with the Fick principle. Systemic oxygen transport was defined as the product of arterial oxygen content and systemic blood flow. Central venous hemoglobin and hematocrit (Coulter S-plus IV), arterial blood gas (Corning 178 analyzer) and rectal temperature were measured in each patient.

Exchange transfusion. Isovolumic partial exchange transfusion was performed using 20 ml/kg of warmed packed red blood cells, and was intended to increase hemoglobin concentration without altering intravascular volume. The procedure was performed in 10 to 15 ml aliquots, by means of a central venous catheter and took approximately 20 minutes to complete. All hemodynamic measurements described were made in duplicate over a 20 to 30 minute period before and 20 minutes after the partial exchange transfusion. The entire study was completed before angiography.

Statistics. The data were evaluated for statistical significance using a two-tailed t test for paired observations. Values are expressed as mean ± standard error of the mean.

Results

Effect on right to left shunt and arterial oxygenation. Table 1 highlights the pertinent data obtained before and after isovolumic partial exchange transfusion. After transfusion, central hemoglobin concentration increased from 13.7 ± 0.5 to 16.4 ± 0.4 g/100 ml, and hematocrit increased from 41.9 ± 1.4 to 50.0 ± 1.2% ($p < 0.001$). The magnitude of right to left shunting diminished in every patient after partial exchange transfusion (Fig. 1). For the group as a whole, the right to left shunt decreased by 59% from 1.44 ± 0.29 to 0.59 ± 0.10 liters/min per m^2 ($p < 0.01$). Effective pulmonary blood flow increased by 17% from 2.72 ± 0.10 to 3.17 ± 0.10 liters/min per m^2 ($p < 0.01$). Systemic blood flow tended to decrease after transfusion, but the change did not reach statistical significance ($p = 0.08$). A significant increase in systemic oxygenation was noted because arterial oxygen saturation increased from 84.3 ± 2.3 to 90.9 ± 1.3% ($p < 0.002$), and arterial P_{O_2} increased from 55.0 ± 3.5 to 62.0 ± 4.1 mm Hg ($p < 0.01$). Despite the tendency for systemic blood flow to decrease, systemic oxygen transport increased from 658.2 ± 47.5 to 737.9 ± 45.4 ml/min per m^2 ($p < 0.002$). The mixed venous oxygen saturation increased from 64.3 ± 3.1 to 71.9 ± 2.3% ($p < 0.001$).

Effect on systemic pressure and resistance. Aortic mean pressure increased from 66.0 ± 3.0 to 76.9 ± 3.7 mm Hg and aortic systolic pressure from 89.1 ± 4.5 to 101.7 ± 4.5 mm Hg ($p < 0.001$). Right atrial mean pressure increased from 1.6 ± 0.7 to 2.6 ± 1.0 mm Hg ($p < 0.05$). Systemic vascular resistance increased in each patient from a mean of 15.9 ± 1.1 to 20.0 ± 1.4 units ($p < 0.01$). A significant relation ($y = 20.44x^{0.32}$, $r = 0.90$, $p < 0.01$) was found between the percent increase in systemic resistance and the percent decrease in right to left shunt (Fig. 2). In addition, a linear relation ($y = 0.36x + 2.88$, $r = 0.83$, $p < 0.02$) was found between the percent increase in systemic resistance and the percent increase in systemic arterial P_{O_2} (Fig. 3).

Finally, increasing the hemoglobin concentration in these children did not significantly affect heart rate, oxygen consumption, arterial pH, partial pressure of carbon dioxide (P_{CO_2}) or rectal temperature. These findings suggest that the children remained in a steady state condition throughout the study.

Discussion

In 1948, Taussig (3) advocated the use of repeated small blood transfusions in children with cyanotic heart disease when hemoglobin concentration was "moderately low." She stated that although the child's cyanosis might increase, the transfusion would "make him stronger." Others (4,5) also described clinical improvement after iron therapy or blood transfusion in hypoxemic children with a hemoglobin concentration in the normal range (some because of iron deficiency). In children with cyanotic heart disease, a hemoglobin concentration in the low to normal range has been referred to as relative anemia (4,5). Although the term implies a physiologic handicap, the hemodynamic consequences of relative anemia have not been well evaluated.

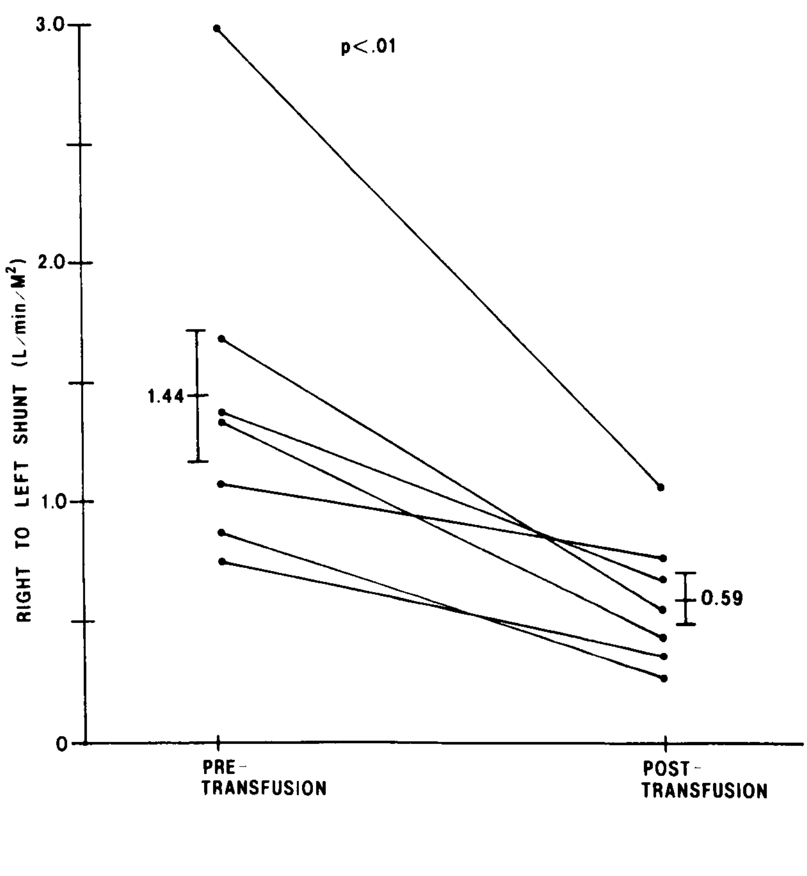

Figure 1. Effect of blood transfusion and subsequent increased hemoglobin concentration on right to left shunting. An average 59% decrease was observed after partial exchange transfusion.

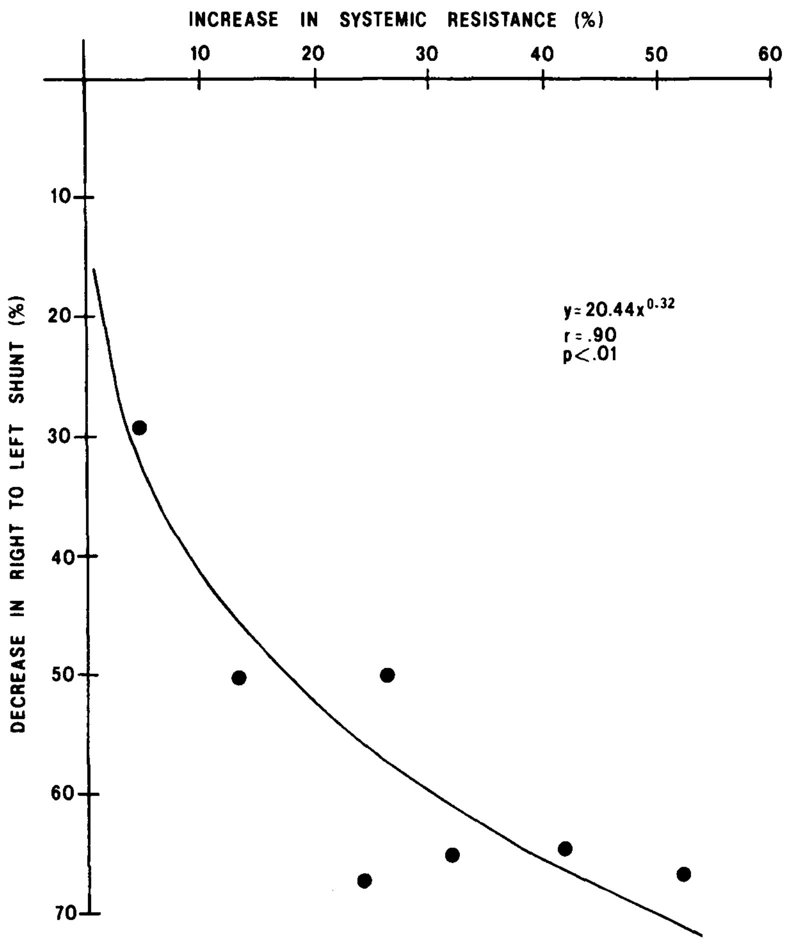

Figure 2. Relation between the increase in systemic vascular resistance and the decrease in right to left shunt after partial exchange transfusion. Values are expressed as percent change.

The present investigation was designed to evaluate the short-term hemodynamic response to increasing hemoglobin concentration in children with a right to left ventricular shunt and relative anemia.

Beneficial effects of increasing hemoglobin concentration. We found that in seven children with a right to left ventricular shunt and a hemoglobin of less than 15 g/100 ml, increasing the hemoglobin concentration not only augments blood oxygen-carrying capacity, but promotes several beneficial hemodynamic changes. In response to an increase in hemoglobin from 13.7 to 16.4 g/100 ml, right to left shunting decreased, effective pulmonary blood flow

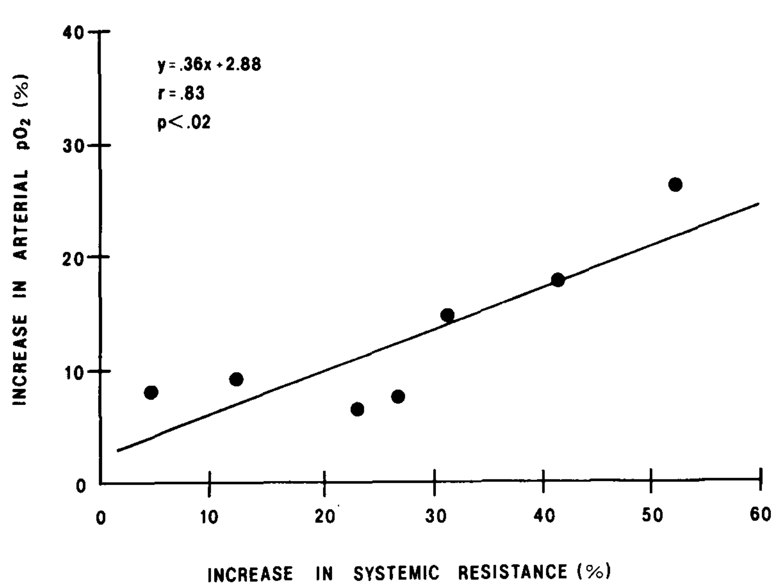

Figure 3. Relation between the increase in systemic vascular resistance and the increase in systemic arterial partial pressure of oxygen (Po_2). Values are expressed as percent change.

increased and systemic arterial oxygen saturation and Po_2 increased significantly. Despite a slight decrease in systemic blood flow, systemic oxygen transport increased appreciably. These acute hemodynamic changes appear to be related to the increase in systemic resistance after partial exchange transfusion (Fig. 2 and 3).

Relation between hemoglobin concentration and systemic vascular resistance. This has been well documented (9–11) and demonstrated in children with congenital heart disease (5,12,13). Changes in hemoglobin concentration alter systemic resistance primarily by affecting blood viscosity (4,12,14,15). The relation between viscosity and resistance, in turn, can be approximated by the Poiseuille equation (16). In addition to its effect on viscosity, the increased hemoglobin concentration in our patients may have promoted an increase in systemic resistance by improving arterial oxygenation. The systemic vasoconstrictor effect of oxygen has been demonstrated in children with congenital heart disease (17), although the mechanism involved remains unclear.

Effect of increased systemic vascular resistance on right to left ventricular shunt. In our study, the decrease in right to left shunt after partial exchange transfusion was found to correlate with the associated increase in systemic vascular resistance (Fig. 2). Apparently, in children with a right to left ventricular shunt and a stenotic but patent right ventricular outflow tract, an increase in systemic resistance opposes right to left shunting and promotes a commensurate increase in pulmonary blood flow. These findings are consistent with previous studies demonstrating that the magnitude of a right to left ventricular shunt is responsive to changes in systemic vascular resistance. In patients with tetralogy of Fallot, a decrease in systemic resistance has been shown to increase both right to left shunting and arterial hypoxemia (12,18–20). Conversely, diminished right to left shunting and improved arterial oxygenation have been demonstrated after the administration of phenylephrine (21), methoxamine (18) and angiotensin (22). Thus, an increase in systemic vascular resistance appears to promote beneficial hemodynamic changes in patients with tetralogy of Fallot. Our study suggests that increasing the hemoglobin concentration may provide a physiologic means of achieving these ends in children with a right to left ventricular shunt and relative anemia.

Effect on blood oxygen-carrying capacity. In addition to its effect on right to left shunting, an increased hemoglobin concentration may have benefited these children by increasing blood oxygen-carrying capacity. The beneficial effects of an increased oxygen-carrying capacity in this setting may be twofold. First, without any change in arterial oxygen saturation or systemic blood flow, the increase in arterial oxygen content would improve systemic oxygen transport. Second, since oxygen consumption did not change, the increased arterial oxygen content would lead to an increased mixed venous oxygen content. This, in turn, would improve arterial oxygenation by increasing the oxygen content of shunted blood, even if right to left shunting remained constant.

Optimal hemoglobin concentration in cyanotic children. The optimal hemoglobin concentration for children with cyanotic heart disease has yet to be determined. In theory, such a hemoglobin concentration would provide for optimal oxygen delivery to the tissues without causing excessive blood viscosity (15). The present study was limited to the acute setting, and the long-term effects of partial exchange transfusion were not evaluated. Nevertheless, these acute data suggest that the optimal hemoglobin concentration for children with a right to left ventricular shunt is greater than 15 g/100 ml. In the seven children studied, increasing the hemoglobin from 13.7 to 16.4 g/100 ml resulted in acute hemodynamic improvement characterized by decreased right to left shunting, increased effective pulmonary blood flow and improved systemic oxygen transport. In these children, a hemoglobin concentration of less than 15 g/100 ml was hemodynamically suboptimal and, therefore, can justifiably be referred to as relative anemia. In contrast, previous studies (5,12) have clearly demonstrated that hyperviscosity associated with a hematocrit above 65% (hemoglobin > 22 g/100 ml) poses a hemodynamic liability for children with cyanotic heart disease. Taken together, these data suggest that the optimal hemoglobin concentration for such children is between 15 and 22 g/100 ml. The precise concentration of hemoglobin that would be optimal for the individual pediatric patient remains difficult to define, however, and probably changes in time with such variables as activity, autonomic tone and the degree of right ventricular outflow obstruction.

Clinical implications. On the basis of the findings of the present study, we recommend that the hemoglobin concentration be kept above 15 g/100 ml in children with hypoxemia caused by a right to left ventricular shunt. The hemoglobin level should be monitored closely in these children, and appropriate therapy instituted (for example, iron supplementation) if it falls below 15 g/100 ml. Any significant blood loss, such as may occur with cardiac catheterization or surgery, should be replaced promptly to avoid potential hemodynamic deterioration. Finally, the present data support the concept that blood transfusion may play an important role in the management of an acute cyanotic spell in a child with tetralogy of Fallot whose hemoglobin level is not excessive. Caution should be exercised, however, in transfusing blood in a patient whose right to left ventricular shunt relates to elevated pulmonary vascular resistance since there is evidence indicating that an increased hemoglobin concentration may promote a disproportionate increase in pulmonary vascular resistance under some circumstances (13).

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